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| EXAMINER | |
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| ISSAC, ROY P | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/673,888 | EVANS ET AL. | |
| | Examiner | Art Unit | |
| | Roy P. Issac | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2,3 and 6-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3 and 6-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This application claims priority under 35 U.S.C § 119(e) from the provisional application 60/414,948 filed on 9/30/2002. However, priority for claim 18 is determined to be the filing date of this application, 9/29/2003 since the provisional application does not provide support for compounds of claim 18.

In further consideration of references of record the Office Action dated 4/19/2007 is withdrawn. In view of the new rejections the finality of that action is withdrawn.

This Office Action is in response to Applicant's response (remarks/Argument/ Amendment to the claims) filed 17 January 2007, wherein claims 2, 3, 6, 7, 9, 10, 12-15 and 17-18 were amended, claims 1, 4 and 5 were cancelled and claims 19-29 were newly added.

### Rejections Withdrawn

As indicated above, applicant's arguments/response filed 17 January 2007 cancelled claims 1, 4 and 5. All rejections made with respect to the cancelled claims, 1, 4 and 5, in the previous office action are withdrawn.

The objection under 37 CFR 1.75 with respect to claims 1 and 17 as substantial duplicates of each other is withdrawn, since claim 1 is cancelled.

The rejection under 35 USC 112 first paragraph, with respect to claims 1-18 in regards to scope of enablement for the prevention of hypercalcemia and for the treatment of any disorder associated with calcium homeostasis is withdrawn since the applicants have cancelled claim 1 and the amended claims do not recite prevention of

hypercalcemia, and the claims as amended are directed to the treatment of specific disorders recited in claims 2 and 3.

The rejection under 35 USC 112 second paragraph, with respect to claims 1-18 is withdrawn since the phrase "disorder of calcium homeostasis" is deleted from claims 3, 17 and 18.

The rejection of claims 2-3, 6-8, 17-21 under section 103(a) over Doll et. al. in view of Eskens et. al. has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made as discussed below.

The following are new or modified grounds for rejection:

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The two compounds of claim 18 are not described or disclosed in the specification as filed. As such, the specification does not provide adequate written description support of claim 18 herein.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-16 and 22-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a combination of a compound of formula I-81 with calcitrol, calcitonin, NPS R-568, and NPS R-467 for treating malignancy-associated hypercalcemia or humoral hypercalcemia of malignancy in a subject, does not reasonably provide enablement for a method of treating one of the other diseases listed in claim 9 with a combination of compounds of formula 1-81 with any compound described as "a second compound for treating" one of the diseases listed in claim 9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are drawn to the method for the treatment of disorders associated with calcium homeostasis. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention:

The claimed invention is a therapeutic method for preventing or treating a disorder of calcium homeostasis.

The relative skill of those in the art:

The relative skill of those in the art is high, with a typical practitioner having obtained a PhD, M.D. or equivalent advanced degree.

The breadth of the claims:

The current claims are deemed very broad since they include the combination of any compound used for the treating one of the disorders listed in claim 9 with one of the compounds of formulas 1-81. The compound to be combined includes all known drugs used for the treatment of said diseases as well as the ones to be developed in the future.

The amount of direction or guidance presented and the presence or absence of working examples:

There are no methods or examples of using any compound other than the compound of Formula I, out of the 81 compounds listed in claim 2 is given. There are no examples or methods for the use of any compounds in combination with any compounds is given. The specification contains a general description of compounds to be used in combination therapy. (Specification, Page 22, lines 20-35). However, this description does not include any specific examples or any general guidelines as to how a combination is to be formulated to enable one of skill in the art to practice the invention without further experimentation.

The examples 1-2 relates to the study of toxicity of the compound of Formula I. Note that the compound of Formula I is a well-known pharmaceutical in clinical use. Example 2 involves the microscopic evaluation of rats that were given the compound of formula I, which shows that the parathyroid glands are affected by the administration of said compound. However, the examples do not indicate that the rats were suffering from any particular disorders associated with calcium homeostasis. Furthermore, the diseases listed has very diverse etiology. For example, osteoporosis is a disease of progressive decrease in bone density. It is not clear how increasing the calcium excretion level will help reduce the loss of calcium density of the skeletal system. One of skill in the art would think increasing the calcium excretion would have the opposite effect of speeding up the progression of osteoporosis. In fact, calcium supplements are recommended for those at risk for osteoporosis. (Merck Manual of Medical Information, Home Ed. Pages 238-240; PTO-892). While osteoporosis is a slow progressing disease that reduce bone density, hypercalcemia of malignancy is a fast setting

condition associated with many of the commonly occurring cancers. Hypercalcemia of malignancy is considered an oncologic emergency that is associated with a median life expectancy of 30 days. (Pearl et. al., Oncology Update, 1996, Pages 163-166; PTO-892). It is conceivable that in such an emergency situation, lowering calcium levels with excretion is helpful, only if it is not achieved by increasing bone resorption. The examples disclosed herein shows that calcium excretion is increased. However, the specification doesn't address whether such excretion is achieved at the expense of lowering bone density. If the increase in calcium excretions is achieved by extracting calcium from bone mass, it is certainly the opposite of what a patient with osteoporosis would hope to achieve.

On the other hand, familial benign hypocalciuric hypercalcemia is a syndrome of lifelong hypercalcemia inherited as an autosomal dominant trait. (Heath et. al. West J. Med. 1994, 160, 554-561; PTO-892). Hypercalcemia of malignancy is an oncologic emergency that is associated with a median life expectancy of approximately 30 days. (Pearl et. al., Oncology update, 1996, 163-166). The etiology of hypercalcemia of malignancy is multifactorial with at least four putative mechanisms, and mechanism varies with tumor type and stage of disease. (Pearl et.al., Page 163, Column 2). First, local bone resorbing factors are though to mediate the hypercalcemial observed in hematologic malignancies. Second, bony metases from solid tumors produce localized osteolysis that may result in hypercalcemia of malignancy. Third, parathyroid hormone related proteins secreted by tumor mimic the renal effects of parathyroid hormone and impair hormone excretion.

There are no examples of any compound in combination with anycompounds of formula 1-81 or compounds of claim 18 for the treatment of any particular diseases listed in claim 9. The lack of working examples is a critical and crucial factor to be considered, especially in cases involving an unpredicatable and undeveloped art. See MPEP § 2164.

The predictability or lack thereof in the art and the quantity of experimentation necessary:

Combination therapy, and drug-drug interactions are known in the art to have various effects, and when physicians use several drugs in combination, they face the problem of knowing whether a specific combination in a given patient has the potential to result in an interaction, and if so, how to take advantage of the interaction if it leads to improvement in therapy or how to avoid the consequences on an interaction if they are adverse. A potential drug interaction refers to the possibility that one drug may alter the intensity of the pharmacological effects of another drug if given concurrently. The net result may be enhanced or diminished effects of one or both of the drugs, or the appearance of new effects, which is not seen with either drug alone. The frequency of significant beneficial or adverse effects is unknown. The interaction between the drugs may be pharmacokinetic, i.e. alteration of the absorption, distribution, or elimination of one drug by another, or may be pharmadynamic, i.e. interactions between agonists and antagonists at drug receptors. The most important drug-drug interactions occur with drugs that have serious toxicity and low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences. Additionally, drug-

drug interactions can be clinically important if the disease being controlled with the drug is serious or potentially fatal if left under treated. Drugs are known to interact at any point during their absorption, distribution, metabolism, or excretion; the result being an increase or decrease in concentration of the drug at the site of action. As individuals vary in their rates of disposition of an given drug, the magnitude of an interaction that alters pharmacokinetic parameters is not always predictable, but can be very significant. See Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 10th Edition, McGraw-Hill Medical Publishing Division, 2001, pages 54-56 (Of Record). Thus, the teachings of the book clearly support that the instant claimed invention, administering a combination of a compound of formulas 1-81 with any compound used for treating one of the disorders disclosed in claim 9 is highly unpredictable.

The usefulness of one compound to have an effect on the calcium homeostasis or for the treatment of one of diseases claimed herein, does not mean that compound and all similar compounds are useful for combination therapy with one of the known drugs used to treat such diseases.

In particular, one skilled in the art would need to know whether the regular administration of the combination in the claimed form over the long term would adversely affect the health of the subject.

In order to answer these questions, in the absence of any existing data, one skilled in the art, will have to undertake laboratory and clinical studies involving different combinations of one of the compounds of formulas 1-81 and one of any of a large series of compounds used to treat one of the diseases listed in claim 9. Accomplishing such a

task for the myriad of symptoms that can be considered associated with calcium homeostasis would require an undue amount of experimentation for the practice of full range of the claimed invention.

*Genentech*, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, especially the breadth of the claims, the unpredictability of the art, and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for the combination therapy claimed herein absent undue experimentation.

Claims 9-16 and 22-29 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating malignancy-associated hypercalcemia or humoral hypercalcemia of malignancy, does not reasonably provide enablement for the treatment of familial benign hypocalciuric hypercalcemia or neonatal severe primary hyperparathyroidism or renal secondary hyperparathyroidism or osteoporosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure

would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

See above rejection for a discussion of wands factors 1, 2, 3, and 4.

The predictability or lack thereof in the art:

See discussion above of the predictability of pharmaceutical arts.

The breadth of the claims and the amount of direction or guidance presented:

The claims are directed to six particular diseases with varying etiology. For example familial benign hypocalciuric hypercalcemia is a syndrome of lifelong hypercalcemia inherited as an autosomal dominant trait. (Heath et. al. West J. Med. 1994, 160, 554-561; PTO-892). On the other hand, Hypercalcemia of malignancy is an oncologic emergency that is associated with a median life expectancy of approximately 30 days. (Pearl et. al., Oncology update, 1996, 163-166). The etiology of hypercalcemia of malignancy is multifactorial with at least four putative mechanisms, and mechanism varies with tumor type and stage of disease. (Pearl et.al., Page 163, Column 2). First, local bone resorbing factors are though to mediate the hypercalcemial observed in hematologic malignancies. Second, bony metases from solid tumors produce localized osteolysis that may result in hypercalcemia of malignancy. Third, parathyroid hormone related proteins secreted by tumor mimic the renal effects of

parathyroid hormone and impair hormone excretion. The experiments herein describe the administration of compound of Formula I to normal rats without hypercalcemia. The administration results in increased excretion of calcium and a lowering of PTH levels. From the increased excretion level and lower PTH level, the results herein seems to follow the third pathway. However, it is not clear form the disclosure how the increased excretion is achieved. Furthermore, there is no indication as to how or whether the compounds of formulae 1-81 can effectively treat a genetic disorder or hypercalcemia of malignancy caused by one of the other pathways.

The presence or absence of working examples:

There are no working examples of the treatment of the particular diseases claimed herein. The disclosed studies involve the administration of one compound from the 83 compunds claimed herein, compound of formula I to normal mice in which calcium excretions were increased. However, there is showing that any disease state can be treated by the compounds herein. There is no showing of how the increased calcium excretions were achieved.

The lack of working examples is a critical and crucial factor to be considered, especially in cases involving an unpredicatable and undeveloped art. See MPEP § 2164.

The quantity of experimentation necessary:

In order to determine whether the compounds of formulae 1-81 are useful for the treatment of one of the diseases of claim one, one of skill in the art would have develop particular disease models and test each of the compounds herein for efficacy in treating

each disease state. Such studies involve substantial intellectual input as well as research and development by highly trained principal scientists.

Thus, the specification fails to provide clear and convincing evidence in sufficient support for the use of compounds of formulae 1-81 or the compounds of claims 18 for the treatment of the many diverse diseases claimed herein.

*Genentech*, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the *Wands* factors as discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in ***undue experimentation*** to practice the invention commensurate in scope with the claims.

Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification as originally filed does not describe any methods of making or using compounds of claim 18. Since the compounds of claim 18, even though retains the structural tricyclic core do have additional functionalities, which would not have been readily apparent to one of skill in the art. The provisional application from which this application depends does not claim nor describe the compounds of claim 18. See

above rejections for the analysis of Wands factors. In view of the wands analysis of unpredictability in the pharmaceutical arts, lack of any working examples of either of the compounds of claim 18 for making or using the compounds as claimed, the diverse etiology of the various disease conditions claimed, and the complete lack of guidance to make and use the compounds of claim 18, one of skill in the art would have to commit to substantial research and development including participation by principal scientists, clinicians and a vast number of support staff to design organic synthetic methodology as well as to test compounds for physiological and biochemical properties. Therefore, in view of the ***Wands*** factors as discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in ***undue experimentation***.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 recites the limitation "wherein the level of $Ca^{2+}$" in lines 1-2, page 17. There is insufficient antecedent basis for this limitation in the claim.

The following are modified rejections necessitated by Applicant's amendment filed 1/17/2007, wherein the limitations in pending claims 2, 3, 6, 7, 9, 10, 12-15 and 17-18 have been changed, and new claims 19-29 have been added, and all claims depend

from amended claims 2 and 3. The limitations in the amended claims have been changed and the breadth and scope of all claims have been changed. Therefore, rejections from the previous Office Action, filed 9/20/2006, have been modified and are listed below.

Claims 10 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims herein appear to have trademarks/abbreviation (AMG 073, NPS 467 for example) in the claims. Applicant is advised that full chemical names should be used in claims. Under 35 U.S.C 112 it is improper to use an acronym without defining it first within claims. Where a trademark or trade name or abbreviation is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C 112, second paragraph. See *Ex parte Simpson*, 218 USPQ (Bd. App. 1982). Appropriate correction is required.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-3 and 6-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Doll et. al. (Of Record) in view of Pearl et. al. (Oncology Update, 1996, 3(5), 1996,

163-166; PTO-892) further in view of (Merck Manual of Diagnostics, Home Ed. 1997, Pages 738-739; PTO-892)

Doll et. al. teaches each of the compounds 1-81 of the instant application for the treatment of several cancers. Tricyclic compounds of Formulae 1-81 of the instant application are disclosed. (Doll et. al, WO/97/23478; Page 15, lines 1-15 and; Page 2 line 10 to Page 13, line10). Doll et. al. further discloses the use of said compounds in patients and with pharmaceutically acceptable carriers. (Page 115, line 5 to Page 116 line 5). Doll et. al further discloses the use of compounds of Formulae 1-81 for the treatment of a variety of cancers that account for majority of the commonly occurring cancers including lung cancer, pancreatic cancers, thyroid follicular cancer, colon cancers, myeloid leukemias, bladder cancer, myelodysplastic syndrome, epidermal cancers, prostate cancers and breast cancers. (Page 116, lines 4-10; Page 15, last paragraph to Page 16, first pargraph). Doll et. al. further discloses tablet formation. (Page 88).

Doll et. al. does not expressly disclose the use of compounds of formulae 1-81 for the treatment of malignancy associated hypercalcemia or humoral hypercalcemia of malignancy or a combination of one of the compounds of formulae 1-81 with another compound.

Pearl et. al. discloses that hypercalcemia of malignancy is an oncologic emergency that occurs in nearly 50% of patients with multiple myeloma or breast cancer. (Page 163, Column 1, Paragraph 2). Patients with lung and epidermoid cancers also have a significant incidence of hypercalcemia. For two reasons, a large

portion of patients with hypercalcemia of malignancy are expected to be treated with compounds of Formulae 1-81 based on the disclosure of Doll et. al. One, Doll et .al. discloses the use of compounds of formulae 1-81 for the treatment of a large number of cancers, particularly ones that have high incidences of hypercalcemia of malignancy. Two, hypercalcemia of malignancy can only occur in patients with cancers, and Doll et. al. discloses the use of compounds of Formulae 1-81 for the treatment of a large number of commonly occurring cancers. Pearl et. al. further disclose several therapies for the treatment of hypercalcemia of malignancy such as saline rehydration and the use of calcitonin. (Page 164, Columns 2-3).

Merck Manual of Diagnostics,notes that people with cancer often have hypercalcemia. A variety of cancers including lung and kidney cancers are disclosed to often result in hypercalcemia. (Page 739, Column 1, paragraph 4).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to treat patients with hypercalcemia of malignancy with a compound of formulae 1-81 since hypercalcemia of malignancy is often present in breast and lung cancers as well as in cancers in general and Doll et. al. discloses the use of compounds of Formulae 1-81 for the treatment of breast and lung cancers as well as a variety of cancers that are commonly occurring. Since a large portion of patients with hypercalcemia of malignancy are expected to receive compounds of formula A as treatment for cancer the benefit of lowering calcium levels is achieved by the same or similar patient population. The patient population in Doll et al. is deemed to anticipate, overlap, or coincide the patient in this claimed invention, in need of such a

treatment of hyperparathyroidism, malignancy-associated hypercalcemia or humoral hypercalcemia of malignancy.

Furthermore, it would have been obvious to one of ordinary skill in the art to combine two treatment regiments such as commonly used drug calcitonin or 1, 25-dihydrovitamin D to achieve beneficial cumulative effects in the treatment of hypercalcemia of malignancy. It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Therefore, one of ordinary skill in the art would have reasonably expected that the benefit of lowering calcium levels in a patient with hypercalcemia of malignancy would have occurred from the treatment of a patient with cancer with a compound of formulae 1-81. Furthermore, one of ordinary skill in the art would have expected that a composition comprising one compounds of formulae 1-81 in combination with calcitonin would have had beneficial cumulative effects in the treatment of a patient with hpercalcemia of malignancy.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Claims 9-16 and 23-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Doll et. al. (Of Record) in view of Eskens et.al. (Of Record) further in

view of applicant's admission regarding the relation between farnesyl transferase inhibitors and disorders of calcium homeostasis. (Specification, Page 3, lines 8-15), further in view of Nemeth et. al. (Of Record).

The disclosure of Doll et. al. is discussed above.

Doll et. al. does not explicitly disclose a combination of a compound Formulae 1-81 with a second compound used for for the treatment of familial benign hypocalciuric hypercalcemia, or neonatal severe primary hyperparathyroidism or renal secondary hyperparathyroidism or osteoporosis or malignancy associated hypercalcemia or humoral hypercalcemia of malignancy.

Nemeth et. al. discloses the use of compounds NPS R-568, and NPS R-467 as useful for the treatment of calcium homeostasis related disorders. (Page 4040, Abstract). Nemath further discloses said compounds for the treatment of osteoporosis and hyperparathyroidism. (Page 4040, Column 2, Paragraph 3).

Applicant admits that 10-20% of cancer patients suffer from parathyroidism. (Specification, Background of the invention, Page 2, 17-25). Applicant further admits of the relation between Farnesyl protein and disorders associated with calcium homeostasis. (Specification, Page 3, lines 8-15). Farnesylation inhibitor B-1086 has been used to treat malignancy associated hypercalcemia. (Specification, Page 3, lines 8-15).

Eskens et. al. discloses that Ras oncogenes and Ras oncoproteins are found with high frequency in various human tumour types and that enzyme farnesyl transferase is involved in the activity of Ras. (Page 319, First Paragraph). One of the

diseases associated with Ras tumours is malignancy associated hypercalcemia. (Eskens, Page 324, Column 1, Paragraph 4). Compound SCH 66336 is well known for its activity as an inhibitor of farnesyl transferase. (Eskens, Page 327, Figure 6 and Tables 1-2).

It would have been obvious to one of ordinary skill in the art to use one of the compounds of formulae 1-81 in combination with another compound used for the treatment of disorders associated with calcium homeostasis including osteoporosis and hyperparathyroidism, or to administer two drugs simultaneously or non-simultaneously. It is considered well within the capabilities basic skills of one of ordinary skill in the art to determine the time of administration of two drugs.

One having ordinary skill in the art would have been motivated to do this because compounds of Formula A are well known for their inhibitory activity against Farnesyl transferase and Farnesyl transferase is well known for its involvement in disorders of calcium homeostasis, and NPS R-568 and NPS R-467 are well known for the treatment of disorders associated with calcium homeostasis such as osteoporosis and hyperparathyroidism.

It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Thus, one of ordinary skill in the art would have reasonably expected that a composition comprising compounds of Formula A and NPS-R-568 and NPS-R-$67 would have had improved activity against disorders of calcium homeostasis. Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

No Claim is allowed.

This rejection is made NON-FINAL due to the new/modified grounds of rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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SAJ 8/3/07

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